Convergent Functional Genomics of Schizophrenia: From Comprehensive Understanding to Genetic Risk Prediction

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Abstract:

We have used a translational convergent functional genomics (CFG) approach to identify and prioritize genes involved in schizophrenia, by gene-level integration of genome-wide association study (GWAS) data with other genetic and gene expression studies in humans and animal models. Using this polyevidence scoring and pathway analyses, we identify top genes (DISC1, TCF4, MBP, MOBP, NCAM1, NRCAM, NDUFV2, RAB18, as well as ADCYAP1, BDNF, CNR1, COMT, DRD2, DTNBP1, GAD1, GRIA1, GRN2B, HTR2A, NRG1, RELN, SNAP-25, TNIK), brain development, myelination, cell adhesion, glutamate receptor signaling, G-protein coupled receptor signaling and cAMP- mediated signaling as key to pathophysiology and as targets for therapeutic intervention. Overall, the data is consistent with a model of disrupted connectivity in schizophrenia, resulting from the effects of neurodevelopmental environmental stress on a background of genetic vulnerability. In addition, we show how the top candidate genes identified by CFG can be used to generate a genetic risk prediction score (GRPS) to aid schizophrenia diagnostics, with predictive ability in independent cohorts. The GRPS also differentiates classic age of onset schizophrenia from early onset and late-onset disease. We also show, in three independent cohorts, two European-American (EA) and one African-American (AA), increasing overlap, reproducibility and consistency of findings from SNPs to genes, then genes prioritized by CFG, and ultimately at the level of biological pathways and mechanisms. Lastly, we compared our top candidate genes for schizophrenia from this analysis with top candidate genes for bipolar disorder and anxiety disorders from previous CFG analyses conducted by us, as well as findings from the fields of autism and Alzheimer. Overall, our work maps the genomic and biological landscape for schizophrenia, providing leads towards a better understanding of illness, diagnostics, and therapeutics. It also reveals the significant genetic overlap with other major psychiatric disorder domains, suggesting the need for improved nosology.